

An appendix to this paper contains copies of the amended claims with markings to show changes made. Deletions are bracketed and insertions are underlined.

Response to Rejection under 35 U.S.C. § 102

Claims 69-72 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Kwon et al., 12 Pharm. Res. 192 (1995) (hereinafter, "Kwon").

Claims 69-72 have been canceled. Therefore, the rejection of these claims under 35 U.S.C. § 102(b) has been obviated.

Response to Rejection under 35 U.S.C. § 103

Claims 63-84 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kwon in view of Unger et al. '430.

Before responding directly to the issues raised by the Examiner under Section 103, the legal foundation for sustaining such a rejection will be reviewed. Briefly, an applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. 35 U.S.C. §§ 102, 103. It is the Patent Office's duty to establish that the applicant is not entitled under the law to a patent. *In re Warner*, 154 USPQ 173, 177 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). Thus, the burden is on the Patent Office to establish a *prima facie* case

of obviousness. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). If no *prima facie* case of obviousness is established, then a rejection under Section 103 cannot properly be sustained. *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). If the Patent Office establishes a *prima facie* case of obviousness, then the burden of production shifts to the applicant to provide appropriate rebuttal, although the burden of persuasion always remains with the Patent Office. *Id.* Such rebuttal may include arguments, amendments, and/or presentation of objective indicia of nonobviousness. However, such objective indicia are always relevant to a determination of nonobviousness whether or not a *prima facie* case of obviousness has been established. *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987). To establish a *prima facie* case of obviousness, the Examiner must show all of the limitations of the claimed invention in the prior art. *In re Ehrreich*, 200 U.S.P.Q. 504, 509-11 (C.C.P.A. 1979). The subject matter of the invention must be considered as a whole and through the eyes of a hypothetical person of ordinary skill, not expert skill, in the relevant art at the time the invention was made. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983). References must also be considered as a whole, including subject matter that teaches away from the invention as well as subject matter that suggests the invention, and not for their isolated teachings. *Ashland Oil, Inc. v. Delta Resins &*

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*Refractories, Inc.*, 227 U.S.P.Q. 657, 669 (Fed. Cir. 1985). References may be combined if there is a suggestion, motivation, or incentive in the prior art to make such a combination. *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc); *In re Jones*, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992). It is not permissible to use hindsight to pick and choose among isolated teachings in the art after first having read Applicant's application to learn the pattern of the invention. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Finally, all the facts in evidence are evaluated, and patentability is determined on the totality of the record. *In re Corkill*, 226 USPQ 1005, 1008 (Fed. Cir. 1985). Factual determinations made by the PTO must be based on a preponderance of the evidence, and legal conclusions must be correct. *In re Caveny*, 226 USPQ 1, 3 (Fed. Cir. 1985).

Pursuant to established legal authority, patentability under 35 U.S.C. § 103 requires a four-step analysis, which involves determining (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed inventions, (3) the level of skill in the art, and (4) the objective evidence of nonobviousness that may have been presented. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 311, 314 (Fed. Cir. 1983). After all of these factors have been considered, the ultimate legal conclusion on the issue of obviousness must be reached. With the

above background in mind the rejections under 35 U.S.C. § 103 will be discussed.

Kwon discloses entrapment of adriamycin, i.e., doxorubicin, in micelles composed of an AB block copolymer (polyethylene oxide-co- $\beta$ -benzyl L-aspartate (PEO-PBLA)).

Unger '430 discloses cationic lipid compounds for use as carriers in intracellular delivery of bioactive agents. Unger '430 also states that these cationic lipid compounds can be formed into vesicular lipid formulations, such as liposomes and micelles. Unger '430 further states that bioactive agents can be mixed with the vesicular lipid formulations. Still further, Unger '430 states that vesicular lipid formulations containing the bioactive agent can be administered to an animal. Moreover, Unger '430 states that energy, such as ultrasonic energy, can be applied to a target tissue for identifying the location of the vesicles or for effecting release of the bioactive agent and facilitating uptake of the bioactive agent.

Applicants respectfully submit that Unger '430 fails to disclose or suggest that ultrasound would be effective for delivery of a hydrophobic drug from a micelle containing a hydrophobic core. Unger '430 teaches and suggests that cationic lipids are used as carriers for delivery of negatively-charged agents, particularly nucleic acids. Although Unger '430 discloses a long laundry list of bioactive agents that purportedly can be delivered using the

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cationic lipid carriers, a person of ordinary skill in the art would recognize that many of the listed bioactive agents would be incompatible with the cationic lipid carriers. (For example, positively charged bioactive agents would be repelled by the positive charges on the cationic lipids. The hydrophilicity of the positive charges on the cationic lipids would also tend to repel hydrophobic molecules. (Therefore, it is respectfully submitted that Unger '430 fails to teach or suggest that ultrasound can be used in connection with any and all types of micelles, for example, hydrophobic drugs. (Therefore, it is respectfully submitted that the combination of Kwon and Unger '430 fails to disclose or suggest each and every limitation of the presently claimed invention, namely the delivery of hydrophobic drugs using AB-diblock copolymers having a hydrophobic core as micellar drug carriers.

It is further respectfully submitted that the Examiner appears to be saying that the combination of Kwon and Unger '430 would make it obvious to deliver all drugs contained in all micelles by using ultrasound. Applicants respectfully submit that this is application of the "obvious to try" standard of making a determination under Section 103, which is improper according to applicable law. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Accordingly, Applicants respectfully submit that the combination of Kwon and Unger '430 is an improper combination

of references, which does not render the presently claimed invention obvious.

For these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Response to Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner further rejected claims 63-84 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, i.e. for filing to comply with the "written description" requirement.

The written description requirement of § 112, first paragraph was reviewed and summarized by the Federal Circuit in *Vas-Cath Inv. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117, 1119 (Fed. Cir. 1991) (emphasis in original) as follows:

[W]e hereby reaffirm . . . that 35 U.S.C. § 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. . . . [T]he proper test is whether the [written description] conveyed with reasonable clarity to those of ordinary skill that [the applicant] had in fact invented the [invention] recited in those claims.

The test, then, is whether the specification conveyed with reasonable clarity to those of ordinary skill that Applicants had in fact invented the methods of delivering a hydrophobic drug as recited in the claims.

The written description makes reasonably clear how hydrophobic-hydrophilic block copolymers are very attractive drug carriers. The specification states, however, that only a few known block copolymers form micelles in aqueous solution. "Among them, AB-type block copolymers and ABA-type triblock copolymers deserve special attention." Page 2, lines 3-15 (citations omitted).

Claims 1, 9, 17, and 25 as originally submitted all recited "micellar drug carrier having a hydrophobic core." It will be recognized that such micellar drug carriers include AB-diblock and ABA-triblock copolymers.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement states: "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." In other words, the claims do not have to be supported by identical words in the specification, but claim limitations must be supported through express, implicit, or inherent disclosure. The specification clearly discloses that micellar drug carriers having a hydrophobic core is part of the invention. The specification clearly discloses that AB-diblock and

ABA-triblock copolymers are micellar drug carriers with hydrophobic cores. Therefore, the specification conveys with reasonable clarity to those skilled in the art that Applicants were in possession of the methods now claimed, where the micellar drug carriers with hydrophobic cores are AB-diblock copolymers.

In view of the above, withdrawal of the rejection under the written description requirement of Section 112, first paragraph, is respectfully requested.

#### Conclusion

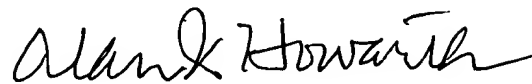
Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicants respectfully request reconsideration and allowance of Claims 63-64, 66-68, 74-75, 77-81, and 83-85 and passage of this application to issue.



DATED this 12<sup>th</sup> day of February, 2003.

Respectfully submitted,



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Version with Markings to Show Changes Made

Please cancel claims 65, 69-73, 76, and 82.

Please amend or rewrite the claims such that they read as follows:

63. (Amended) A method for delivery of a hydrophobic drug to a selected site in a patient comprising:

(a) administering to said patient a composition comprising a micellar drug carrier comprising a hydrophobic core and an effective amount of said hydrophobic drug disposed in said hydrophobic core, wherein said micellar drug carrier is an AB-diblock copolymer; and

(b) applying ultrasonic energy to said selected site such that said hydrophobic drug is released from said hydrophobic core to said selected site.

66. (Amended) The method of claim [65] 63 wherein said hydrophobic drug is an anthracycline.

74. (Amended) A method for enhancing uptake of a hydrophobic drug by cells at a selected site in a patient comprising:

(a) administering to said patient a composition comprising a micellar drug carrier comprising a hydrophobic core and an effective amount of said hydrophobic drug disposed in said

hydrophobic core, wherein said micellar drug carrier is an AB-diblock copolymer; and

(b) applying ultrasonic energy to said selected site such that said hydrophobic drug is released from said hydrophobic core and taken up by said cells.

77. (Amended) The method of claim [76] 74 wherein said hydrophobic drug is an anthracycline.

80. (Amended) A method for reducing side effects in a patient from administration of a hydrophobic drug comprising:

(a) administering to said patient a composition comprising a micellar drug carrier comprising a hydrophobic core and an effective amount of said hydrophobic drug disposed in said hydrophobic core, wherein said micellar drug carrier is an AB-diblock copolymer; and

(b) applying ultrasonic energy to said patient such that said hydrophobic drug is released from said hydrophobic core.

83. (Amended) The method of claim [82] 80 wherein said hydrophobic drug is an anthracycline.